REMARKS

The Official Action of July 26, 2007, and the prior art relied upon therein have been carefully studied. The claims in the application are now claims 10-21, and these claims define patentable subject matter warranting their allowance. Accordingly, the applicants respectfully request favorable reconsideration and allowance.

The priority acknowledgement appearing near the bottom of the Office Action Summary has been noted. Applicants understand that the PTO is acknowledging receipt of all of applicants' papers required under Section 119, and applicants are proceeding in reliance thereof.

Claims 1-7 have been rejected under the first paragraph of Section 112. The rejection is respectfully traversed.

While claims 1-7 have now been deleted and have been replaced by a new set of method claims, applicants nevertheless respectfully submit that the rejection is unjustified because the present specification provides a more than sufficient description regarding the use of a colony-stimulating factor (CSF) for the treatment of renal disease.

First, as is acknowledged by the PTO in the rejection, the specification states that "This model is considered to be nephropathy model because of strong evidence of tubular damage and thyroidization in the kidney. The renal injury of this model mainly includes tubular atrophy or partial necrosis, showing ischemic renal injury resembling clinical atherosclerotic nephropathy or diabetes-induced atherosclerotic nephropathy" (refer to page 15, lines 10-16).

The tubular damage is also considered to be a pathology in acute and chronic renal failure. The applicants submit herewith a copy of Molitoris et al, *Kidney International* (2004) 66, 496-499. It states that "The pathophysiology of ischemic acute renal failure (ARF) involves a complex interplay between renal hemodynamics, tubular and endothelial cell injury, and inflammatory processes" (refer to page 496, left column, lines 2-5). Therefore, tubular damage is a pathology of acute renal failure.

Regarding chronic renal failure, the applicants submit a copy of Nangaku, *Internal Medicine,* Vol. 43, No. 1, 9-17 (January 2004). It states that "Thus, it is widely recognized that tubulointerstitial injury serves as an important mediator and a final common pathway of chronic kidney failure" (Refer to page 9, right column, lines 14-16). It also states that "Tubulointerstitial injury is a final common pathway leading to end-stage renal failure" (refer to page 14, "Summary and Conclusion", the first sentence). Therefore, it should be absolutely clear that tubular damage is pathology of renal failure.

In the present invention, it is confirmed that G-CSF reduced tubular damage, i.e. provided an improvement. The result shows that CSF is effective for the treatment of not only clinical atherosclerotic nephropathy and diabetes-induced atherosclerotic nephropathy, but also renal failure.

As applicants' specification would certainly enable those skilled in the art to practice the invention as broadly as it is claimed, applicants respectfully request withdrawal of the rejection.

Claims 1-9 have been rejected as anticipated by Hanes et al USP 5,855,913 ("Hanes"). This rejection is respectfully traversed.

Claim 10 has not been so rejected. Claims 1-9 have now been replaced by method claims. As Hanes does not disclose treatment of any renal disease by the administering of CSF, applicants need not respond to this rejection at the present time.

In the absence of claims 1-9, applicants request withdrawal of the rejection.

Claims 1-10 have been rejected under Section 102 as anticipated by Shishido et al, Citation AB ("Shishido"). Claims 1-10 have also been rejected under Section 102 as being anticipated by Pierce et al USP 6,689,351 ("Pierce"). These rejections are respectfully traversed.

As regards claims 1-9, applicants need not reply at the present time in view of the deletion of claims 1-9, as noted above in conjunction with the rejection based on Hanes.

As regards claim 10[1] (and possibly new claims 11-21), applicants respectfully submit that neither Shishido nor Pierce discloses (or even makes obvious) any method for treating renal disease by administering CSF.

Claim 10 relates to a method for proliferating or regenerating renal tissue or a cell present in renal tissue by contacting G-CSF with the renal tissue or the cell present in renal tissue. This is not done by either Pierce or Shishido.

Shishido relates to a study of the effects and pharmacokinetics of rhG-CSF on the treatment of neuthropenia in patients with renal failure, and it states "... in

[1] The recitation added at the end of claim 10 finds support, for example, at page 1, lines 15-18 of applicants' specification.

conclusion, rhG-CSF was considered to be an effective and safe therapeutic agent for neutropenia and neutrophil dysfunction in patients with renal failure" (see the title and the second sentence from the bottom of the abstract). Neutropenia and neutrophil dysfunction are of course not renal disease. Namely, Shishido merely discloses that rhG-CSF can be used for the treatment of neutropenia and neutrophil dysfunction, not for the treatment of any renal disease as called for in claims 11 and 12, and certainly not for the conditions recited in the dependent claims such as claims 13-17. The invention of applicants is directed to a method for treating a renal disease comprising administering an effective amount of a colony-stimulating factor (CSF), and is not related to neutropenia and neutrophil dysfunction. It is clear that the applicants' invention is not anticipated by Shishido.

Pierce discloses a method for promoting accelerated wound healing in an injured patient comprising topical administration of granulocyte macrophage-colony stimulating factor (GM-CSF) (see claim 1). Clearly, the invention of Pierce is entirely different from the applicants' invention.

Applicants respectfully submit that the application of Pierce against claim 10 is a very substantial stretch. There is no disclosure in Pierce having anything to do with renal tissue. If the rejection is based on alleged inherency, then applicants must point out that the law is clear that for inherency to be applicable in a rejection based on prior art, the inherency must be **reasonably certain**. There is no reasonable certainty in Pierce of the treatment of any renal tissue.

Withdrawal of the rejections based on Shishido and Pierce is respectfully requested.

Claims 1, 2, 8 and 9 have been rejected under Section 102 as anticipated by Fukuda et al U.S. published application 20004/00019184 ("Fukuda"). This rejection is respectfully traversed.

Claim 10 has not been so rejected. Claims 1, 2, 8 and 9 have now been replaced by method claims. As Fukuda does not disclose treatment of any renal disease by the administration of the CSF, applicants need not respond to this rejection at the present time.

However, it may be noted for the record that Fukuda relates to a method for treating ischemic disease by administering a combination of G-CSF and hepatocyte growth factor (HGF), which contributes to vascular genesis in the patient so treated for ischemic disease (paragraph [0058]). It therefore should be clear that Fukuda has nothing to do with the treatment of renal disease.

Claims 1-3 and 5-10 have been rejected as obvious under Section 103 from Bruder et al USP 6,355,239 ("Bruder") in view of Bonnem et al USP 5,679,356 ("Bonnem"), further in view of the publication of Nicholls. This rejection is respectfully traversed.

Applicants believe and respectfully submit that even in retrospect, a consideration of the three citations together would not lead one of ordinary skill in the art to the present invention.

Bruder teaches the use of allogenic mesenchymal stem cells in treating anemia. The portion which was pointed out by the examiner (column 10, lines 12-23) merely discloses that human mesenchymal stem cells having a gene encoding erythropoietin incorporated therein would help resolve the anemia. Namely, such portion only teaches that erythropoietin

would increase erythrocytes. Although such portion also includes the expression: "Other encoded cytokines can be G-CSF or GM-CSF, for example", this does not mean that G-CSF or GM-CSF is useful in the treatment of anemia.

The treatment suggested by Bruder has nothing to do with the treatment claimed, and the relationship to renal failure is only indirect. Bruder thus uses a quite different method than the present invention for treating anemia, not for treating renal failure. Bruder does not disclose or teach the present invention in any form.

Bonnem relates to a method for enhancing an immune response to a vaccine by administering GM-CSF in conjunction with a vaccine. Namely, it relates to the use of GM-CSF as a vaccine adjuvant. It does not disclose or teach that GM-CSF itself is useful in the treatment of renal diseases.

Certainly the gene therapy proposed by Bruder and the method of Bonnem for enhancing the immune response to a vaccine by administering GM-CSF in conjunction with a vaccine have no relationship to one another. The person of ordinary skill in the art would have had no reason to even begin to consider these two citations in combination.

Nicholls merely describes the pathology of atherosclerotic renovascular disease, and is entirely silent about the method of the present invention.

Again, the Nicholls' proposal has nothing to do with the treatment of renal disease, but only relates to atherosclerotic renovascular disease on diabetic patients who have suffered renal failure. It therefore focuses on a problem which occurs on diabetic renal failure, but not on the renal failure itself. Applicants believe and respectfully submit that there is nothing in Nicholls, Bonnem and Bruder that would have caused a person of ordinary skill in the art

to try to even begin to pick out bits and pieces from each of these to combine in any way so as to reach the present invention.

There would have been no reason to combine or even attempt to combine the citations for any reason, and certainly not to accomplish the present invention.

Moreover, applicants have actually confirmed that administering G-CSF alone was very effective in the treatment of renal disease. The present invention would not have been obvious from Bruder in view of Bonnem and Nicholls, and the rejection should be withdrawn. Such is respectfully requested.

The prior art documents of record and not relied upon by the PTO have been noted, along with the implication that such documents are deemed by the PTO to be insufficiently material to warrant their application against any of applicants' claims.

Applicants believe that all issues raised in the Official Action have been addressed above in a manner that should lead to patentability of the present application. Favorable consideration and early formal allowance are respectfully requested.

Respectfully submitted,
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